Increasing severity of cardiovascular risk factors with increasing middle cerebral artery stenotic involvement in Type 2 diabetic Chinese patients with asymptomatic cerebrovascular disease

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Short title: Risk factors for middle cerebral artery stenosis

Word counts: abstract 185, text 2,107

Keywords: blood pressure, glucose, middle cerebral artery stenosis, metabolic syndrome, Type 2 diabetes mellitus.

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Abstract

Background: Conventional risk factors contribute to the pathogenesis of ischaemic stroke and differences in the pattern of these may explain the heterogeneity of disease presentation in different populations. In Chinese, middle cerebral artery (MCA) stenosis is the most commonly identified intracranial vascular lesion.

Objectives: To identify determinants associated with increasing severity of MCA stenosis in asymptomatic Chinese Type 2 diabetic patients with and without MCA stenosis determined using transcranial Doppler.

Methods: Anthropometric and fasting biochemical parameters were compared between Type 2 diabetic patients with MCA stenosis in 1 (n=185) or both (n=200) vessels and 1492 without evidence of stenosis.

Results: Increasing MCA stenotic vascular involvement was associated with significantly increasing age, duration of diabetes, systolic blood pressure, and LDL-cholesterol, but with lower glucose levels. There was also increased prevalence of hypertension, dyslipidaemia and use of blood pressure and glucose-lowering agents in the patients with MCA stenosis. Concomitant significant increases in prevalence of peripheral vascular disease and retinopathy were also observed in the patients with MCA stenosis.

Conclusions: In these asymptomatic Type 2 diabetics a number of cardiovascular risk factors were closely associated with MCA stenosis.

Introduction

Stroke is a major cause of mortality and morbidity in Oriental populations, with the World Health Organisation estimating 1.6 million stroke-related deaths in China alone in 2000, and rates are predicted to increase as the population ages (1). In China in 1999, mortality resulting from stroke (137.7/100,000) was second only to that due to malignancy (2). Improved control of risk factors has led to a reduction in age-adjusted stroke mortality rates, but as the population ages, absolute rates are rising.

In Oriental populations, apart from Singapore, higher mortality is attributed to stroke than in Caucasian populations where coronary heart disease generally predominates (3,4). However, even within China there is a great variability in stroke rates, which are generally higher in urban than in rural populations and in the North relative to the South. For instance in 1986 the annual age-standardised incidence of stroke was 234.4 in Jilin Province in the north-east vs. 53.2 per 100,000 population in Guangdong in southern China (5). The north-south differences were in part due to the increased prevalence of hypertension in the North with a 10% increase in prevalence of hypertension being associated with a 2.7-fold higher incidence of stroke (5). These studies support the importance of environmental and lifestyle factors in the aetiology of stroke.

Stroke is a heterogeneous disorder with marked ethnic differences in the distribution of arterial lesions. Intracerebral haemorrhage has been reported to be 2-3 times more frequent in Chinese than in Caucasian populations, accounting for 20-30% of strokes (6). In 114 non-selected autopsy subjects from Hong Kong intracranial was found to be most severe than extracranial stenosis (7). In Hong Kong, of 705 consecutively recruited stroke patients, occlusive arteries were found in 345 patients (49%), 37% of the total had only intracranial stenosis, 10% tandem lesions and 2.3% only extracranial lesions (8). In Caucasian patients referred for the evaluation of asymptomatic carotid bruits, 39.2% were found to have extracranial carotid stenosis, and only 12.9% were found to have intracranial stenosis (9). In Chinese stenosis of the middle cerebral artery (MCA) was the most common lesion, found in 35.9% of the patients (8). The cerebrovascular lesions tended to be more diffuse rather than discrete as generally observed in

Caucasian populations with over half having two or more (up to nine) lesions. In a population-based study of 590 rural Chinese subjects screened by transcranial Doppler, 7% over 40 years were found to have intracranial stenosis (2). We have previously shown that the presence and extent of vascular lesions independently predicted the risk of stroke or death at 6 months (8). Hypertension, diabetes and a family history of stroke and a history of heart disease were independent predictors of intracranial stenosis with risk increasing substantially with increasing coexisting factors (2). In a clinic-based study of more than 3000 asymptomatic Chinese individuals similar risk factors were identified. Furthermore, the prevalence of intracranial stenosis was up to 25% in those subjects with multiple risk factors (2). In Chinese patients with acute stroke screened for diabetes or impaired glucose tolerance over half were found to have these conditions, many of whom were undiagnosed, with nearly all having ischaemic stroke (10). Interventions that target the modifiable risk factors, such as diabetes and hypertension have been shown to reduce the development of stroke in Chinese subjects (11).

In this study in Type 2 diabetic Chinese subjects asymptomatic for cerebrovascular disease we determined the factors contributing to MCA stenotic vascular involvement, the most common form of cerebrovascular ischaemia in this population.

Methods

The study protocol was approved by the Clinical Research Ethics Committee of the Chinese University of Hong Kong. All 2165 Type 2 diabetic patients, recruited from the diabetes and neurology clinics at the Prince of Wales Hospital, were unrelated and gave written, informed consent. They were of Han Chinese origin, without any known ancestors of other ethnic origin, and were living in the Hong Kong Special Administrative Region of China at the time of the study. Patients were considered diabetic if the fasting plasma glucose was ≥7.8 mmol/L or the two hour post 75g oral glucose tolerance test plasma glucose level was ≥11.1 mmol/L (12) Type 1 diabetic patients (1.7% from an initial 2202 patients recruited) were defined on the basis of acute symptoms

with heavy ketonuria (>3+) or ketoacidosis at diagnosis or requirement for continuous insulin treatment within one year of diagnosis, and were excluded from the study (12) None of the type 2 diabetic patients screened had previously suffered from a stroke.

The patients were examined by transcranial Doppler (EME TC-2000). A single experienced operator (RL) performed all the transcranial Doppler evaluations (Figure). We studied the middle cerebral artery (MCA) using a standardised protocol examining the artery with 4cm increments through the temporal window at 52-64 mm. The criteria for occlusive arteries were defined by an abnormally high peak systolic flow velocity of ≥140 cm/s for the MCA (8). Apart from the above velocity criteria, we took into account the age of patients, presence of turbulence or musical sound, and whether the abnormal velocity was segmental. Where it was not possible for insonation of the cerebral arteries through the temporal window, the patients (13.3% of the total group) were excluded from the analyses. The subjects who were excluded were slightly older (59.8±10.4 vs 54.9±11.3 years), with slightly higher systolic blood pressure (142±22 vs 138±22 mm Hg) and with a lower proportion of males (28.7 vs 40.8%, all $p<0.05$) than those included in the study, but otherwise the remaining conventional cardiovascular risk factors did not differ significantly between the groups. The above diagnostic criteria in our neurovascular laboratory were based on our laboratory references, which had a quality assurance program with supplementary angiographic studies. At our laboratory, we perform >1200 transcranial Doppler examinations each year and had validated our criteria with magnetic resonance angiography (13) and clinical outcome (8).

Measurement of seated blood pressure, anthropometric (waist circumference and body mass index) and plasma biochemical (lipid and glycaemic profiles) parameters taken after an overnight fast were performed as described in detail previously (14). The patients' medications were suspended for the morning of the examination providing assessment of trough levels, therefore assessment of the haemodynamic parameters as continuous variables is not appropriate as some patients were on hypertension treatment. Subjects were defined as hypertensive, if, after 5 minutes rest, their seated systolic blood pressure (SBP) was ≥140 mm Hg and/or diastolic blood pressure

(DBP) ≥90 mm Hg on at least two occasions or they were receiving blood pressure-lowering medication. Patients were assessed to rule out secondary causes of hypertension and renal disease.

Retinopathy was assessed by an ophthalmologist in all the patients. The fundi were examined through dilated pupils and retinopathy was considered to be present if there was one or more areas of haemorrhages, microaneurysms, cotton wool spots and/or laser coagulation scars related to diabetic retinopathy. Symptomatic peripheral vascular disease was diagnosed if claudication, gangrene or ischaemia-related amputation were present. Foot pulses were examined in each patient and the ankle-brachial systolic arterial pressure ratio (ABR) was determined by Doppler examination in those with abnormal pulses. An ABR <0.9 in either leg was considered suggestive and <0.7 confirmatory of PVD (15). Histories of coronary and cerebrovascular disease were recorded, and patients with the latter were excluded.

Data from normally distributed parameters are presented as mean±SD, whereas skewed data were logarithmically transformed and expressed as geometric mean with 95% confidence intervals. Differences in anthropometric and fasting plasma biochemical parameters between those patients with or without MCA stenosis were examined using the analysis of variance. A Bonferroni post hoc test was used to determine differences between the individual groups. Dichotomous variables were compared using the χ^2-test. Gender was coded 0 and 1 for male and female, respectively. Those patients with and without MCA stenoses were coded 0 and 1, respectively. Those variables that correlated with the MCA stenosis were included in the forward conditional linear regression analyses to determine independent predictors of this condition. These variables included age, gender, systolic blood pressure, diagnosis of hypertension, glucose, diagnosis of dyslipidaemia and LDL-cholesterol levels and duration of diabetes. The variables included in the analyses were linearly related to the dependent variable. The Statistical Package for the Social Sciences was used in the analyses (SPSS. version 11.0.1, 2001, SPSS Inc, Chicago, Illinois, USA).

Results

Of the 2165 Type 2 diabetic patients with asymptomatic cerebrovascular involvement the presence or absence of stenosis in the MCA could be determined in 1877 patients, in whom evidence of MCA stenosis was identified in 385 subjects (20.6%). This included 185 (48.1%) with single vessel involvement and the remainder with stenoses in both vessels.

The demographic characteristics and prevalence rates of concomitant disorders of the Type 2 diabetic Chinese patients with or without evidence of middle cerebral artery stenosis are described in Table 1. Age and age of onset of diabetes and duration were significantly higher in those patients with an increasing number of stenotic vessels. Systolic blood pressure, prevalence and treatment of hypertension and total and LDL-cholesterol and prevalence of dyslipidaemia were also significantly increased. Glycosylated haemoglobin A1c did not significantly differ between the three groups, but glucose surprisingly decreased with increasing vascular involvement. However, in contrast the proportion of the patients receiving glucose-lowering therapy increased. A number of other concomitant vascular disorders were also associated with the MCA stenoses, including peripheral vascular disease and retinopathy (Table 1).

Using stepwise multiple regression the presence of hypertension (β=0.11, p=0.003), age (β=0.07, p=0.013), LDL-cholesterol (β=0.08, p=0.003), glucose (β=0.07, p=0.006), and systolic blood pressure (β=0.09, p=0.021) were independent predictors of the presence of the MCA in one or both vessels (MCA stenosis = [0.15·hypertension] + [0.004·age] + [0.06·LDL-cholesterol] – [0.32·glucose] + [0.03·systolic blood pressure]-0.28; R^2=0.067, F=18.2, p<0.001).

Discussion

In Chinese subjects, MCA stenosis is the most commonly identified intracranial arterial lesion (8), and in the current study we investigated Type 2 diabetics, who are particularly prone to vascular disease (16). A total of 20.6% of the Type 2 diabetic subjects were found to have evidence of MCA stenosis in one or both vessels, with the high rate being due to enrichment of the sample with diabetic patients recruited from the general medical and diabetic clinics.

The level of a number of factors were increased with increasing presence of the MCA stenosis, including age, female gender, age at diabetic onset and duration, systolic blood pressure and the presence of hypertension, and LDL-cholesterol, whereas glycaemia decreased, although the prevalence of glucose-lowering treatment increased. Although the age at onset of diabetes increased by 2.7 years this difference is unlikely to be clinically significant.

In the current study, despite a significant decrease in the proportion of male subjects with the number of stenotic MCA, gender was not an independent risk factor after the other conventional risk factors were considered. Although men have a higher incidence of stroke, the longer life expectancy of females results in a greater proportion of females having strokes (4). This may also result from more men dying at younger ages from heart disease, although there was no evidence of survivor bias in the current study, selection bias in the older patients may have occurred.

Age further contributes to the development of hypertension and stroke (4,17), and was an independent predictor of the number of affected vessels in the current study. Age acts as a composite factor associated with a clustering of a number of risk factors. Regression equations function to explain the largest proportion of the variance in the model, rather than identifying biologically relevant parameters involved in the disease pathogenesis. As such composite variables are most likely to be strong independent predictors of the variable of interest. It is also important to remember that exclusion of a parameter does not exclude it from directly contributing to the pathogenesis of the disorder, merely the variance attributed to the parameter is accounted for by other variables.

Type 2 diabetes is closely associated with micro- and macrovascular disease, the major causes of morbidity and mortality in these patients (16), as can be seen by the high prevalence of MCA stenoses in these diabetic subjects. Interventions that lower glycaemia particularly, such as from the UK Prospective Diabetes Study reduced microvascular disease, but not macrovascular disease (18). This finding fits the data from the current study of diabetic patients, however it is not certain why the increasing vascular involvement was associated with slightly, but significantly lower glucose levels. There was an increasing proportion of these patients who were receiving

glucose-lowering therapy that may have contributed to lower glucose levels through better glycaemic control.

It has been suggested that lipid parameters are more closely associated with extracranial and coronary atherosclerosis, and blood pressure with intracranial atherosclerosis (19). However, in the Oslo study LDL-cholesterol was an independent predictor of the development of intracranial atherogenesis, as was seen in the current study. Lipid-lowering studies have clearly confirmed the importance of cholesterol in the pathogenesis of ischaemic stroke. In the Heart Protection Study treatment with simvastatin lowered the risk of ischaemic stroke by 30% compared to placebo (20), and similar observations in the Eastern Stroke and Coronary Heart Disease Study supports such findings (17).

Blood pressure is a major predictor of haemorrhagic and atherogenic forms of stroke (4,17). Hypertension has been reported to be associated with more severe intercranial atherosclerosis, but not in extracranial cerebral vessels, and this is supported by a number of studies (21,22). In the current study, both systolic blood pressure, despite the confounding by treatment, and the proportion of subjects with hypertension were significantly elevated in subjects with MCA stenosis and were independent predictors for the increasing MCA stenotic vascular involvement. The inclusion of both blood pressure-related parameters suggests each contributed additional information in the regression analyses. Hypertension has also been reported as an independent predictor of stroke in other Chinese populations (5). The UK Prospective Diabetes Study highlighted the clear benefits of lowering blood pressure to reduce vascular disease in type 2 diabetic patients (23). Although the relationship between the MCA stenoses and systolic blood pressure was significant, it is likely blood pressure-lowering treatment will have attenuated it. Therefore, the dichotomous classification of hypertension that combines blood pressure levels and treatment status, but which is generally less informative than a continuously distributed parameter, attributes an additional proportion of the variance to blood pressure. Treatment effects on diastolic blood pressure may have similarly limited any relationship, which contrasts with the Oslo study where, despite patients receiving blood pressure-lowering treatment, it has been reported to more

strongly predict fatal stroke than systolic blood pressure (24). As diastolic blood pressure levels were similar between the groups, yet systolic blood pressure increased, pulse pressure also increased and may contribute to the development of cerebrovascular disease in these patients.

In Chinese patients who had experienced acute cerebral ischaemia, the presence of occluded vessels was the strongest predictor of further vascular events or death within 6 months (8). The majority of the subsequent events were strokes rather than from ischaemic heart disease as has been reported in other ischaemic stroke series (8,25). The current data show the close relationship between modifiable cardiovascular risk factors and middle artery stenoses and, by extrapolation, the increased risk of cardiovascular events and highlight the need for coordinated treatment of risk factors to minimise such events.

In summary, a number of conventional cardiovascular risk factors including age, LDL-cholesterol and in particular systolic blood pressure or hypertensive status contributed to increasing MCA stenotic vascular involvement in this group of Type 2 diabetic patients.

Acknowledgement

This work was supported by the Hong Kong Research Grants Council Grant CUHK 4280/97M and CUHK 4095/00M.

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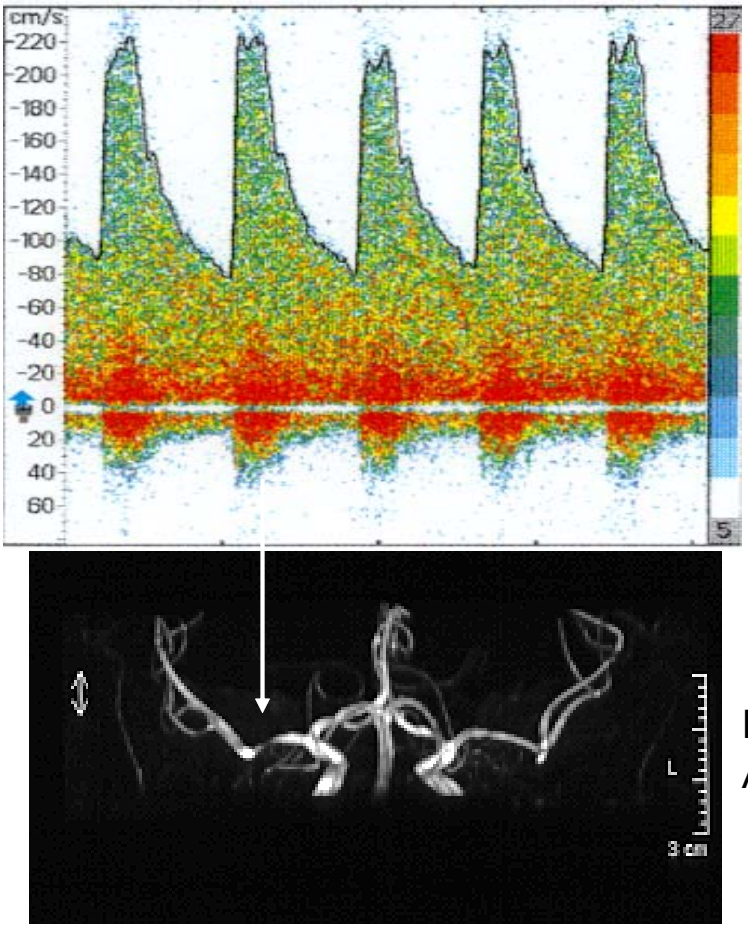
Table 1 Demographic features and prevalence rates of concomitant disorders in the 1877 Chinese Type 2 diabetic patients with and without evidence of middle cerebral artery (MCA) stenosis

Parameters (%)	Middle cerebral artery stenosis			
	None	One vessel	Two vessel	p value
Numbers	1492	185	200	-
Age (years)	54.0±11.4	58.3±10.5*	58.8±10.3*	<0.001
Gender (% Male)	42.2	36.2	35.5	0.031
Duration of diabetes (years)	4.1 (3.8-4.3)	4.6 (3.7-5.8)	5.4 (4.4-6.6)*	0.030
Age of diabetes onset (years)	47.8±11.2	49.6±10.0	50.5±10.8*	0.010
Body mass index (kg/m^2)	24.8±3.7	24.3±3.6	24.4±3.4	NS
Waist circumference (cm)	84.2±9.6	84.7±10.6	85.2±8.2	NS
Systolic blood pressure (mm Hg)	136±21	143±22*	149±24*†	<0.001
Diastolic blood pressure (mm Hg)	80±16	80±12	80±15	NS
Mean arterial pressure (mm Hg)	99±15	101±13	103±14*	0.001
Pulse pressure (mm Hg)	55±20	63±18*	69±20*†	<0.001
Glucose (mmol/L)	8.66 (8.49-8.84)	8.45 (8.02-8.91)	8.06 (7.67-8.48)*	0.039
Glycosylated haemoglobin A_{1c}(%)	7.8±2.0	7.8±1.7	7.6±1.6	NS
Total cholesterol (mmol/L)	5.6±1.1	5.7±1.0	5.8±0.9*	0.012
HDL-cholesterol (mmol/L)	1.26±0.32	1.27±0.32	1.26±0.35	NS
LDL-cholesterol (mmol/L)	3.6±0.9	3.8±0.9*	3.8±0.8*	<0.001
Triglyceride (mmol/L)	1.43 (1.28-1.48)	1.39 (1.28-1.51)	1.44 (1.34-1.56)	NS
Drug treatment of diabetes (%)	78.3	84.3	86.4	0.033
Prevalence of hypertension (Rx) (%)	50.6 (29.8)	71.7* (51.7)*	79.0* (51.9)*	<0.001
Prevalence of dyslipidaemia (Rx) (%)	48.0 (4.5)	54.1 (4.8)	56.4* (3.6)	0.021 (NS)
Peripheral vascular disease (%)	3.4	4.2	9.5*	0.006
History of myocardial infarction (%)	3.1	5.3	4.2	NS
Retinopathy (%)	24.1	27.8	39.6*	0.001
Smoking consumption (ex/current, %)	13.5 / 13.4	11.9 / 12.6	13.8 / 12.0	NS
Alcohol consumption (ex/current, %)	11.7 / 7.2	12.6 / 8.4	13.7 / 7.4	NS

Mean±SD or geometric mean (95% confidence intervals); NS = non-significant, Rx=receiving therapy, p value is for analysis of variance between all three groups, *p<0.05 compared to the no stenosis group, †p<0.05 compared to the single vessel group

Figure: An example of middle cerebral artery stenosis detected by transcranial Doppler ultrasound with a peak systolic velocity up to 220 cm/sec and turbulent flow. The stenosis was confirmed by a magnetic resonance angiography.



Transcranial Doppler

Magnetic Resonance Angiography